

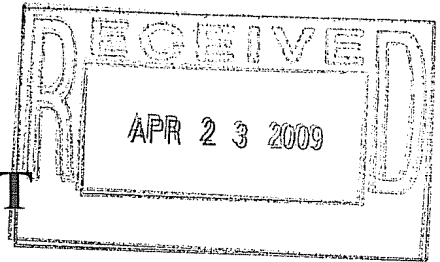
PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: ARLES A. TAYLOR, JR.
JENKINS, WILSON, TAYLOR & HUNT, P.A.
SUITE 1200, UNIVERSITY TOWER
3100 TOWER BOULEVARD
DURHAM, NC 27707

*pending
US case*

PCT



NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 1242/92 PCT	Date of mailing (day/month/year) 21 APR 2009 FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US 09/32824	International filing date (day/month/year) 02 February 2009 (02.02.2009)
Applicant VANDERBILT UNIVERSITY	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 8270

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: <div style="text-align: right;">Lee W. Young</div> <small>PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774</small>
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Form PCT/ISA/220 (January 2004)

(See notes on accompanying sheet)

DOCKET DATES: 5/21; 6/21/09
 ASSIGNED ATTY: AA1/LRL
 FILE NO. 1242 92 PCT
 DOCKETED BY: PER DATE: 4/27/09
#105 due 7/1/09 for 124219212

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 1242/92 PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US 09/32824	International filing date (<i>day/month/year</i>) 02 February 2009 (02.02.2009)	(Earliest) Priority Date (<i>day/month/year</i>) 31 January 2008 (31.01.2008)
Applicant VANDERBILT UNIVERSITY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed.
- ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. 1
- ☒ as suggested by the applicant.
- ☐ as selected by this Authority, because the applicant failed to suggest a figure.
- ☐ as selected by this Authority, because this figure better characterizes the invention.
- b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/32824

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 38/00; A61P 11/00 (2009.01)

USPC - 514/12; 382/132

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/12; 382/132

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic Databases Searched: USPTO WEST (PGPUB, EPAB, JPAB, USPT), Google Patent, Google Scholar. Search Terms Used: bronchopulmonary dysplasia, hypertension, hypoxia, hypocitrullinemia, citrulline level\$, citrulline level\$, intravenous, infant

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2004/0235953 A1 (Summar et al.) 25 November 2004 (25.11.2004) entire document especially para [0229]-[0231]; [0238]; [0383]-[0384]; [0402]	1-19
Y	Schreiber et al. Inhaled nitric oxide in premature infants with the respiratory distress syndrome. N Engl. J. Med., 2003, 349, 2099-20107, especially page 2099	1-8
Y	Berkenbosch et al. Decreased synthesis and vasodilation to nitric oxide in piglets with hypoxia-induced pulmonary hypertension. Am. J. Physiol. Lung Cell. Mol. Physiol., 2000, Vol. 278, L276-L283, especially abstract, page L 281	9-19
A	US 2007/0026448 A1 (Ramanathan et al.) 01 February 2007 (01.02.2007) entire document	1-19

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 September 2009 (17.09.2009)

Date of mailing of the international search report

21 APR 2009

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:
ARLES A. TAYLOR, JR.
JENKINS, WILSON, TAYLOR & HUNT, P.A.
SUITE 1200, UNIVERSITY TOWER
3100 TOWER BOULEVARD
DURHAM, NC 27707

Date of mailing
(day/month/year)

21 APR 2009

Applicant's or agent's file reference
1242/92 PCT

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 09/32824

International filing date (day/month/year)

02 February 2009 (02.02.2009)

Priority date (day/month/year)

31 January 2008 (31.01.2008)

International Patent Classification (IPC) or both national classification and IPC

IPC(8) - A61K 38/00; A61P 11/00 (2009.01)

USPC - 514/12; 382/132

Applicant VANDERBILT UNIVERSITY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Date of completion of this opinion

17 March 2009 (17.03.2009)

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 09/32824

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:
 - a. type of material
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing
 - ☐ contained in the international application as filed
 - ☐ filed together with the international application in electronic form
 - ☐ furnished subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 09/32824

Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement		
1. Statement			
Novelty (N)	Claims	1-19	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-19	NO
Industrial applicability (IA)	Claims	1-19	YES
	Claims	NONE	NO
2. Citations and explanations:			
<p>Claims 1-8 lack an inventive step under PCT Article 33 (3) as being obvious over US 2004/0235953 A1 to Summar et al. (hereafter 'Summar') in view of the article entitled 'inhaled nitric oxide in premature infants with the respiratory distress syndrome' by Schreiber et al. (hereafter 'Schreiber').</p> <p>Regarding claim 1, Summar teaches the administration a nitric oxide precursor, citrulline to increase the presence of nitric oxide in a subject (para [0229]-[0231]). Summar does not teach the administration of citrulline to treat bronchopulmonary dysplasia. However, Schreiber teaches the inhalation of nitric oxide to treat bronchopulmonary dysplasia (chronic lung disease) in premature infants (page 2099, method and conclusion). It would have been prima facie obvious for one of ordinary skill in the art, at the time the invention was made to combine the teachings of Summar and Schreiber to treat bronchopulmonary dysplasia in premature infants.</p> <p>Regarding claim 2, Summar teaches the method, wherein the nitric oxide precursor is selected from the group consisting of citrulline, a precursor that generates citrulline in vivo, arginine, a precursor that generates arginine in vivo, and combinations thereof (para [0230]-[0231]).</p> <p>Regarding claim 3, Summar teaches the method, wherein the administering comprises oral administration, intravenous administration, and combinations thereof. (para [0231]).</p> <p>Regarding claim 4, Summar teaches the method, wherein the subject is an infant (para [0230]).</p> <p>Regarding claim 5, Summar teaches the method, wherein the infant is a preterm infant (para [0230]).</p> <p>Regarding claim 6, Summar teaches the method, wherein the nitric oxide precursor is administered in a dose ranging from about 100 mg to about 30,000 mg (para [0238]).</p> <p>Regarding claim 7, Summar teaches the method, wherein the nitric oxide precursor is administered in a dose ranging from about 250 mg to about 1,000 mg (para [0238]).</p> <p>Regarding claim 8, Summar teaches the method, wherein the subject suffers from hypocitrullinemia characterized by plasma citrulline levels of < 37 micromol/liter (para [0383]-[0384]; [0402]).</p> <p>Claims 9-19 lack an inventive step under PCT Article 33 (3) as being obvious over Summar in view of the article entitled 'Decreased synthesis and vasodilation to nitric oxide in piglets with hypoxia-induced pulmonary hypertension' by Berkenbosch et al. (hereafter 'Berkenbosch').</p> <p>Regarding claim 9, Summar teaches the administration a nitric oxide precursor, citrulline to increase the presence of nitric oxide in a subject (para [0229]-[0231]). Summar does not teach the administration of citrulline to treat chronic hypoxia-induced pulmonary hypertension. However, Berkenbosch teaches neonatal chronic hypoxia-induced pulmonary hypertension is associated with multiple disruptions in the nitric oxide pathway, wherein hypoxia decreases NO production (abstract; page L281, discussion). It would have been prima facie obvious for one of ordinary skill in the art, at the time the invention was made to combine the teachings of Summar and Berkenbosch to treat chronic hypoxia-induced pulmonary hypertension in infants and preterm infants.</p> <p>Regarding claim 10, Summar teaches the method, wherein the nitric oxide precursor is selected from the group consisting of citrulline, a precursor that generates citrulline in vivo, arginine, a precursor that generates arginine in vivo, and combinations thereof. (para [0230]-[0231]).</p> <p>Regarding claim 11, Summar teaches the method, wherein the administering comprises oral administration, intravenous administration, and combinations thereof. (para [0231]).</p> <p>Regarding claim 12, Summar teaches the method, wherein the subject is an infant (para [0230]).</p> <p>(please see continuation in supplemental box)</p>			

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 09/32824

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box V.2 (Citations and Explanations):

Regarding claim 13, Summar teaches the method, wherein the infant is a preterm infant (para [0230]).

Regarding claim 14, Summar teaches the method, wherein the nitric oxide precursor is administered in a dose ranging from about 100 mg to about 30,000 mg (para [0238]).

Regarding claim 15, Summar teaches the method, wherein the nitric oxide precursor is administered in a dose ranging from about 250 mg to about 1,000 mg (para [0238]).

Regarding claim 16, Summar teaches the method, wherein the subject suffers from hypocitrullinemia characterized by plasma citrulline levels of < 37 micromol/liter (para [0383]-[0384]; [0402]).

Regarding claim 17, Summar teaches the pharmaceutical composition comprising a pharmaceutically acceptable carrier and an amount of citrulline effective to raise plasma citrulline level, wherein the level is determined by comparing plasma citrulline levels in a subject (para [0230]; [0383]-[0384]; [0243]-[0244]). Summar does not teach the composition is to treat hypoxia-induced pulmonary hypertension in a subject. However, Berkenbosch teaches neonatal chronic hypoxia-induced pulmonary hypertension is associated with multiple disruptions in the nitric oxide pathway, wherein hypoxia decreases NO production (abstract; page L281, discussion). It would have been obvious for one of ordinary skill in the art, at the time the invention was made to combine the teachings of Summar and Berkenbosch to treat chronic hypoxia-induced pulmonary hypertension in infants and preterm infants.

Regarding claim 18, Summar teaches the pharmaceutical composition, wherein the amount of citrulline effective to raise plasma citrulline level in a subject to at least micromol/liter, optionally at least 10 micromol/liter, optionally at least 20 micromol/liter, optionally at least 25 micromol/liter, and optionally about 37 micromol/liter (para [0383]-[0384]; [0402]).

Regarding claim 19, Summar teaches the pharmaceutical composition, wherein the pharmaceutical composition is adapted for intravenous or oral administration (para [0231]).

Claims 1-19 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.